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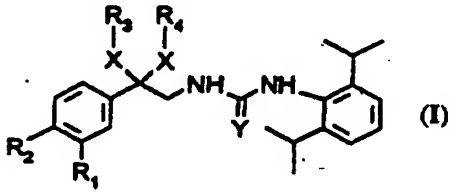
(54) Title: PHOSPHATE DERIVATIVES OF DISUBSTITUTED UREAS AND THIOUREAS

(57) Abstract

The present invention relates to a novel compound having ACAT inhibitory activity of formula (I), wherein: the X substituent, being the same, are O or S; Y is independently O or S; one of R_1 and R_2 is $OPO(OH)_2$ and the other is hydrogen, C_1-C_6 alkyl, halo, hydroxy, C_1-C_4 alkoxy or $OPO(OH)_2$; each of R_3 and R_4, being the same or different, is C_1-C_6 alkyl; or R_3 and R_4, taken together, form a C_2-C_4 alkylene chain in which each carbon atom can be optionally substitued by 1 or 2 substituents independently chosen from halo or C_1-C_3 alkyl; and the pharmaceutically acceptable salts thereof.



(I)

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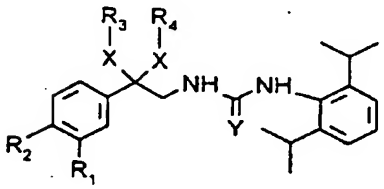
Phosphate derivatives of disubstituted ureas and thioureas

The present invention relates to novel compounds having ACAT inhibitory activity, to a process for their preparation and to pharmaceutical compositions containing them.

The inhibition of the enzime acylCoA:cholesterol acyltransferase is generally considered one of the most appealing approaches to the treatment of dyslipidemias and to the prevention of the atherosclerotic process (Exp. Opin. Invest. Drugs (1994) 3(5) 427-436). ACAT inhibitors are well known in the art, for instance, the inventors of the present invention in EP 0500348 disclosed a new class of urea and thiourea derivatives endowed with high *in vitro* ACAT inhibitory activity. However such urea and thiourea derivatives, similarly to most of the known ACAT inhibitors, were characterized by high lipophilicity, extreme low aqueous solubility and low bioavailability; by consequence their effects on blood and tissutal cholesterol levels were indirect and appeared almost exclusively related to a reduction of the intestinal cholesterol absorption. Recently further experimental data demonstrated that the therapeutic potential of an ACAT inhibitor can be markedly enhanced when the compound directly affects ACAT activity in target tissues such as the liver and the arterial wall (Atherosclerosclerosis and Thrombosis (1994) 149(9) 1498). Therefore a hydrosolubility sufficient to achieve high systemic bioavailability is now considered a crucial requirement for an ACAT inhibitor to be developed as a hypolipidemic as well as an antiatherosclerotic agent. The task to combine in the same molecule a high affinity for ACAT enzime and an adequate hydrosolubility cannot be achieved by merely introducing hydrophilic groups into the structure of *in vitro* active ACAT inhibitors, as this strategy results in most cases in a significant loss of the inhibitory activity.

It has now been discovered that new phosphate derivatives of a selected class of hydroxy compounds embraced by the general formula disclosed in EP 0500348, besides being highly hydrosoluble, are also potent *in vivo* ACAT inhibitors. By virtue of such properties the compounds of the present invention can be useful therapeutic agents in the treatment of dyslipidemias and atherosclerosis.

Accordingly, the present invention provides new compounds having the following general formula (I).



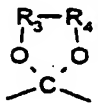
(I)

wherein:

the X substituents, being the same, are O or S;
Y is independently O or S;
one of R_1 and R_2 is $OPO(OH)_2$ and the other is hydrogen, C_1-C_6 alkyl, halo, hydroxy, C_1-C_4 alkoxy or $OPO(OH)_2$;
each of R_3 and R_4, being the same or different, is C_1-C_6 alkyl; or R_3 and R_4, taken together, form a C_2-C_4 alkylene chain in which each carbon atom can be optionally substituted by 1 or 2 substituents independently chosen from halo or C_1-C_3 alkyl;
and the pharmaceutically acceptable salts thereof.

The alkyl and alkoxy groups may be branched or straight groups. Representative examples of C_1-C_6 alkyl groups include methyl, ethyl, *n*- and *iso*-propyl, *n*-, *iso*-, *sec*- and *tert*-butyl. Representative examples of C_1-C_4 alkoxy groups include methoxy or ethoxy. A C_1-C_3 alkyl group is in particular methyl or ethyl. Halo includes fluoro, bromo, chlorine or iodine, in particular chlorine or bromine.

When R_3 and R_4, taken together, are a C_2-C_4 alkylene chain and X is oxygen, then the resulting pentatomic, hexatomic or heptatomic 1,3-dioxalkyl ring is respectively a 1,3-dioxolan, 1,3-dioxan or 1,3-dioxepan ring which may be represented by the formula



wherein R_3-R_4 represents a C_2-C_4 alkylene chain in which each carbon atom can be optionally substituted by 1 or 2 substituents independently chosen from halogen, in particular chlorine or C_1-C_3 alkyl, in particular methyl.

When R_3 and R_4, taken together, are a C_2-C_4 alkylene chain and X is sulfur, then the resulting pentatomic, hexatomic or heptatomic 1,3-dithialkyl ring is respectively a 1,3-dithiolan, 1,3-dithian or 1,3-dithiepan ring which may be represented by the formula

wherein R_3-R_4 represents a C_2-C_4 alkylene chain in which each carbon atom can be optionally substituted by 1 or 2 substituents independently chosen from halogen, in particular chlorine or C_1-C_3 alkyl, in particular methyl.

The pharmaceutically acceptable salts of the compounds of formula (I) include the salts of inorganic bases, for example hydroxides of alkaly metals, e.g. sodium or potassium, or alkaline-heart metals, e.g. calcium or magnesium, and the salts of organic bases organic

bases, such as for example aliphatic amines, e.g. methylamine, ethylamine, diethylamine, trimethylamine, or heterocyclic amines, e.g. piperidine.

The present invention also include within its scope all the possible isomers, stereoisomers, and their mixtures and both the metabolites and the pharmaceutically acceptable bio-precursors (otherwise known as pro-drugs) of the compounds of formula (I).

Preferred compounds of the invention are the compounds of formula (I) wherein:

X is O ;

Y is O ;

one of R_1 and R_2 is $OPO(OH)_2$ and the other is hydrogen;

R_3 and R_4, taken together, are a C_2-C_3 alkylene chain in which each carbon atom can be optionally substituted by 1 or 2 substituents independently chosen from halo or C_1-C_2 alkyl;

and the pharmaceutically acceptable salts thereof.

Examples of preferred compounds of the invention are the following:

4-{2-[3-(2,6-diisopropylphenyl)ureidomethyl]-4,5-dimethyl-1,3-dioxolan-2-yl}phenylphosphate;

3-{2-[3-(2,6-diisopropylphenyl)ureidomethyl]-4,5-dimethyl-1,3-dioxolan-2-yl}phenylphosphate;

3-{2-[3-(2,6-diisopropylphenyl)ureidomethyl]-5,5-dimethyl-1,3-dioxan-2-yl}phenylphosphate;

4-{2-[3-(2,6-diisopropylphenyl)ureidomethyl]-5,5-diethyl-1,3-dioxan-2-yl}phenylphospate;

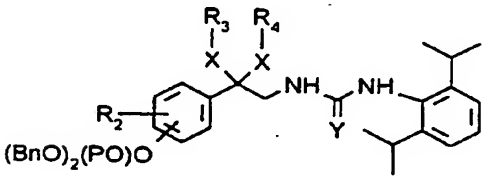
3-{2-[3-(2,6-diisopropylphenyl)ureidomethyl]-5,5-diethyl-1,3-dioxan-2-yl}phenylphospate;

and

4-{2-[3-(2,6-diisopropylphenyl)ureidomethyl]-5,5-dimethyl-1,3-dioxan-2-yl}phenylphospate;

if the case either as a single isomer or as a mixture of isomers thereof, and the pharmaceutically acceptable salts thereof.

The compounds of the invention and the salts thereof can be obtained by a process comprising the hydrogenolysis of a compound of formula (II)



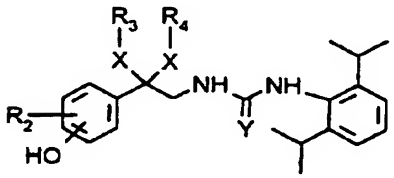
(II)

wherein Bn means benzyl and R_2, R_3, R_4, Y and X are as defined above by reaction with hydrogen in the presence of a catalyst; and, if desired, converting a compound of formula (I) into another compound of formula (I), and/or resolving a mixture of compounds of

formula (I) into the single isomers and/or converting a compound of formula (I) into a pharmaceutically acceptable salt thereof.

The hydrogenolysis reaction of a compound of formula (II) to obtain a compound of formula (I) can be carried out according to well known methods in the art. For instance the reaction can be performed in a suitable organic solvent e.g. methyl alcohol, at room temperature, in the presence of a hydrogenation catalyst such as e.g. palladium on chaorcal or platinum black under a low pressure e.g. from 1 to 5 atm of hydrogen.

The compounds of formula (II) can be prepared from the corresponding hydroxy derivatives of formula (III)



(III)

wherein R_2, R_3, R_4, Y and X are as defined above, by reaction with dibenzylpyrophosphate in an opportune organic solvent such as e.g. dimethylformamide or acetonitrile in the presence of a base such as e.g. potassium tert-butylate or sodium hydride at a temperature ranging from 0 to 50°C, according to well known procedures.

Hydroxy compounds of formula (III) can be prepared as described in EP 0 500 348 A1.

The separation of a mixture of isomers of a compound of the invention into single isomers and the conversion of a compound of formula (I) into a pharmaceutically acceptable salt thereof can be carried out according to well known methods in the art.

Pharmacology

The compounds of the present invention show inhibitory activity of the enzyme acyl CoA:cholesterol acyltransferase (ACAT-EC 2.3.1.26) which regulates the intracellular esterification of cholesterol (J.Lip. Res. (1985) **26** 647) and thus the intracellular accumulation of cholesteryl esters. The activity of this enzyme increases to the greatest extent during the atherosclerotic process in which the accumulation of esterified cholesterol in the atherosclerotic plaque is one of the predominant events (B.B.A. (1980) **617** 458). By virtue of their water solubility, compounds of the present invention, contrary to those disclosed in EP 0500348, can be included into injectable preparations; therefore they can reach high plasmatic levels, that are useful for the direct and efficient inhibition of the liver and aortic enzyme. By this systemic ACAT inhibitory activity, the compounds of the present invention, besides having antidyslipidemic activity, can also act as direct antiatherosclerotic agents, able to inhibit the development of the atheromatous plaque, and

therefore they are useful in particular for the prevention of coronary heart disease (CHD), e.g. myocardial infarction and angina.

Biological results

The representative compound of the present invention (-)-4-{(4R, 5R)2-[3-(2,6-diisopropyl-phenyl)ureidomethyl]-4,5-dimethyl-1,3-dioxolan-2-yl}phenylphosphate monosodium salt (internal code FCE 28654A) showed a good water solubility (8.5 mg/ml were dissolved into a pH 7.4 PBS buffer) in comparison with the compounds disclosed in EP 0 500 348 A1 such as e.g. N-[2,6-bis(1-methylethyl)phenyl]-N'-(2-cyclohexyl-1,3-dithiolan-2-yl)methylurea (internal code FCE 27612) or N-[2,6-bis(1-methylethyl)phenyl]-N'-(2-cyclohexyl-5,5-dimethyl-1,3-dioxan-2-yl)methylurea (internal code FCE 27356) whose water solubility in the same conditions is less than 0.1mg/ml. The compound FCE 28654A was tested *in vivo* in hypocholesterolemic rats according to the following experimental procedure: male rats (mean weight 300 g) were treated with a 1.5% cholesterol - 0.5% cholic acid diet for 5 days. FCE 28654, dissolved in sterile PBS at pH 7.4, was then intravenously administered through the tail vein. Six hours after dosing animals were sacrified and blood and hepatic (after extraction into chloroform/methanol according to the method of Folch [*J. Biol. Chem.* **1957**, *226*, 497]) lipids were dosed by enzymatic methods. The results presented in the table indicate that the representative compound FCE 28654 significantly reduces plasmatic cholesterol levels in hypercholesterolemic rats after a single intravenous administration at the dose of 2 mg/kg.

Table Effects of a single intravenous administration of compound FCE 28654A on plasma lipids of hypercholesterolemic rats.

Treatment	Plasma lipids (mg/dl)[a]			
	FC	CE	TG	PL
Control	65±18	226±51	109±35	178±30
FCE 28654A	39±10*	134±36**	126±34	138±19*

a) Values are mean ± SD n = 7 * $p < 0.05$, ** $p < 0.01$ (Dunnett's test).
FC = free cholesterol, CE = cholesterol esters, TG = triglycerides, PL = phospholipids.

The dosage level suitable for administration to adult humans depends on the age, weight, conditions of the patient and on the administration route; for example, the dosage adopted for oral administration e.g. for the representative compound of the invention FCE 28654A may range from about 10 to about 500 mg pro dose, from 1 to 5 times daily.

The compounds of the invention can be administered in a variety of dosage forms, e.g. orally, in the form of tablets, capsules, sugar or film coated tablets, liquid solutions or suspensions; rectally in the form of suppositories; parenterally, e.g. intramuscolarly, or by intravenous injection or infusion.

The invention includes pharmaceutical compositions comprising a compound of the invention in association with a pharmaceutically acceptable excipient (which can be a carrier or a diluent).

The pharmaceutical compositions containing the compounds of the invention are usually prepared following conventional methods and are administered in a pharmaceutically suitable form.

For example, the solid oral forms may contain, together with the active compound, diluents, e.g. lactose, destrose, saccharose, cellulose, corn starch or potato starch; lubricants, e.g. silica, talc, stearic acid, magnesium or calcium stearate, and/or polyethylene glycols; binding agents, e.g. starches, arabic gums, gelatin, methylcellulose, carboxymethylcellulose or polyvinyl pyrrolidone; disaggregating agents, e.g. a starch, alginic acid, alginates or sodium starch glycolate; effervescing mixtures; dyestuffs; sweeteners; wetting agents such as lecithin, polysorbates, laurylsulphates; and, in general, non-toxic and pharmacologically inactive substances used in pharmaceutical formulations. Said pharmaceutical preparations may be manufactured in known manner, for example, by means of mixing, granulating, tabletting, sugar-coating, or film-coating processes.

The liquid dispersion for oral administration may be e.g. syrups, emulsions and suspension.

The syrups may contain as carrier, for example, saccharose or saccharose with glycerine and/or mannitol and/or sorbitol.

The suspension and the emulsion may contain as carrier, for example, a natural gum, agar, sodium alginate, pectin, methylcellulose, carboxymethylcellulose, or polyvinyl alcohol.

The suspension or solutions for intramuscolar injections may contain, togethr with the active compound, a pharmaceutically acceptable carrier, e.g. sterile water, olive oil, ethyl oleate, glycols, e.g. propylene glycol, and, if desidered, a suitable amount of lidocaine hydrochloride. The solutions for intravenous injections or infusion may contain as carrier, for example, sterile water or preferably they may be in the form of sterile, acqueous, isotonic saline solutions.

The suppositories may contain together with the active compound a pharmaceutically acceptable carrier, e.g. cocoa butter, polyethylene glycol, a polyoxyethylene sorbitan fatty acid ester surfactant or lecithin.

The following examples illustrate but do not limit the invention.

Example 1 *Preparation of (-)-4-{(4R, 5R)2-[3-(2,6-diisopropyl-phenyl)ureidomethyl]-4,5-dimethyl-1,3-dioxolan-2-yl}phenylphosphate monosodium salt (FCE 28654A).*

A mixture of (-)-dibenzyl-4-{(4R, 5R)2-[3-(2,6-diisopropyl-phenyl)ureidomethyl]-4,5-dimethyl-1,3-dioxolan-2-yl}phenylphosphate (0.800g, 1.16mmol) and 10% palladium on activated carbon (0.400g) in 15ml of ethyl alcohol was shacken under a hydrogen pressure of 2 atm at 12°C for 0.25h. Solid catalyst was then filtered, the solvent evaporated under reduced pressure, and the residue partially purified by column chromatography over silica gel (eluent chloroform/methyl alcohol/acetic acid 64:16:20). The phosphate was conveniently isolated as the monosodium salt by adding to the acid in ethyl alcohol 1 equivalent of sodium acetate in acqueous ethyl alcohol. After evaporation of the solvent the residue was taken up with n-hexane/diethyl ether, filtered and dried yielding 450 mg of the title compound as a colorless powder.

mp 142-144°C; $[\alpha]^{23}_{D}$ -13.2 (c = 0.980, MeOH); ^{1}H NMR (400 MHz, DMSO) δ : 1.0-1.04 (18H, m), 3.09 (2H, m), 3.3-3.5 (3H, m), 3.81 (1H, m), 6.1 (1H, bs), 7.0-7.3 (7H, m), 7.5 (1H, bs); FAB MS : 551 (100, $[M+Na]^{+}$), 529 (52.3, $[M+H]^{+}$), 449 (49.1).

Analogously the following products can be prepared :

3-{2-[3-(2,6-diisopropylphenyl)ureidomethyl]-4,5-dimethyl-1,3-dioxolan-2-yl}phenylphosphate;

3-{2-[3-(2,6-diisopropylphenyl)ureidomethyl]-5,5-dimethyl-1,3-dioxan-2-yl}phenylphosphate;

4-{2-[3-(2,6-diisopropylphenyl)ureidomethyl]-5,5-diethyl-1,3-dioxan-2-yl}phenylphosphate;

3-{2-[3-(2,6-diisopropylphenyl)ureidomethyl]-5,5-diethyl-1,3-dioxan-2-yl}phenylphosphate;

and

4-{2-[3-(2,6-diisopropylphenyl)ureidomethyl]-5,5-dimethyl-1,3-dioxan-2-yl}phenylphosphate.

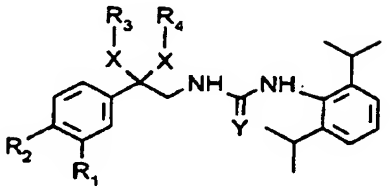
Example 2

With the usual methods of pharmaceutical technique, preparation can be made of capsules having the following composition:

(-)-4-{(4R, 5R)2-[3-(2,6-diisopropyl-phenyl)ureidomethyl]-4,5-dimethyl-1,3-dioxolan-2-yl}phenylphosphate monosodium salt	200mg
talc	8mg
starch	8mg
microcristalline cellulose	23mg
magnesium stearate	5mg

CLAIMS

1. A compound of formula (I)



(I)

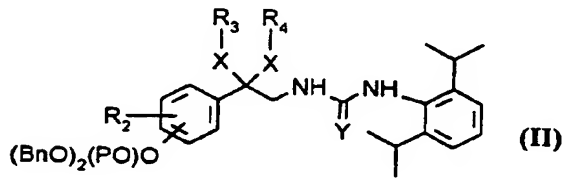
wherein:
the X substituent, being the same, are O or S;
Y is independently O or S;
one of R_1 and R_2 is $OPO(OH)_2$ and the other is hydrogen, C_1-C_6 alkyl, halo, hydroxy, C_1-C_4 alkoxy or $OPO(OH)_2$;
each of R_3 and R_4, being the same or different, is C_1-C_6 alkyl; or R_3 and R_4, taken together, form a C_2-C_4 alkylene chain in which each carbon atom can be optionally substituted by 1 or 2 substituents independently chosen from halo or C_1-C_3 alkyl;
and the pharmaceutically acceptable salts thereof.

2. A compound of formula (I), according to claim 1, wherein:
X is O ;
Y is O ;
one of R_1 and R_2 is $OPO(OH)_2$ and the other is hydrogen;
R_3 and R_4, taken together, are a C_2-C_3 alkylene chain in which each carbon atom can be optionally substituted by 1 or 2 substituents independently chosen from halo or C_1-C_2 alkyl;
and the pharmaceutically acceptable salts thereof.

3. A compound selected from :
4-{2-[3-(2,6-diisopropylphenyl)ureidomethyl]-4,5-dimethyl-1,3-dioxolan-2-yl}phenylphosphate;
3-{2-[3-(2,6-diisopropylphenyl)ureidomethyl]-4,5-dimethyl-1,3-dioxolan-2-yl}phenylphosphate;
3-{2-[3-(2,6-diisopropylphenyl)ureidomethyl]-5,5-dimethyl-1,3-dioxan-2-yl}phenylphospate;
4-{2-[3-(2,6-diisopropylphenyl)ureidomethyl]-5,5-diethyl-1,3-dioxan-2-yl}phenylphospate;

3-{2 [3-(2,6-diisopropylphenyl)ureidomethyl]-5,5-diethyl-1,3-dioxan-2-yl}phenylphospate;
and
4-{2-[3-(2,6-diisopropylphenyl)ureidomethyl]-5,5-dimethyl-1,3-dioxan-2-yl}phenylphospate;
if the case either as a single isomer or as a mixture of isomers thereof, and the pharmaceutically acceptable salts thereof.

4. A process for the preparation of a compound of formula (I) as defined in claim 1, or salt thereof, said process comprising the hydrogenolysis of a compound of formula (II)



(II)

wherein Bn means benzyl and R_2, R_3, R_4, Y and X are as defined in claim 1 and, if desired, converting a compound of formula (I) into another compound of formula (I), and/or resolving a mixture of compounds of formula (I) into the single isomers and/or converting a compound of formula (I) into a pharmaceutically acceptable salt thereof.

5. A pharmaceutical composition comprising a suitable carrier and/or diluent and, as an active principle, a compound of formula (I) as claimed in claim 1, or a pharmaceutically acceptable salt thereof.

6. A compound of formula (I), as defined in claim 1, or a pharmaceutically acceptable salt thereof, for use in the prevention of coronary heart disease.

7. A compound of formula (I), as defined in claim 1, or a pharmaceutically acceptable salt thereof, for use as antidyslipidaemic agent.

8. A compound of formula (I), as defined in claim 1, or a pharmaceutically acceptable salt thereof, for use as antiatherosclerotic agent.

INTERNATIONAL SEARCH REPORT

International Application No
PC., EP 96/00781

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07F9/12 A61K31/66 C07F9/655

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07F A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP,A,0 500 348 (FARMITALIA CARLO ERBA) 26 August 1992 cited in the application see the whole document ---	1-8
A	WO,A,95 04053 (PHARMACIA S.P.A.) 9 February 1995 see the whole document ---	1-8
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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
28 June 1996	03.07.96
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+ 31-70) 340-3016	Authorized officer Beslier, L

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INTERNATIONAL SEARCH REPORT

International Application No
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